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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

PC 101101

2

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

TXR.No. 0051435 ✓

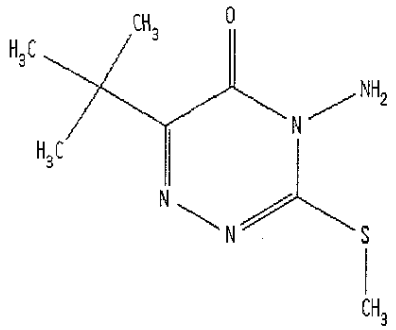
REVISED

1/1/95

Chemical Name: Metribuzin

PC Code: 101101

Structure



The Health Effects Metribuzin
Division Toxicology Endpoint Selection Committee considered the available toxicology data for Metribuzin at a meeting held on June 4, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: Stephen C. Dapson, Ph.D. Date:

SECTION HEAD: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Date:

BRANCH CHIEF: Stephanie R. Irene, Ph.D. Date:

DERMAL ABSORPTION DATA

MRID: Not applicable

% absorbed: No adequate data are available.

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: Developmental Toxicity (Teratology) Study in Rabbits (§83-3b)

MRID No.: 00087796

Summary: In a repeat developmental toxicity (teratology) study, New Zealand white rabbits were given 0, 15, 45, or 135 mg/kg/day of metribuzin by gavage on gestation days 6-18. Maternal toxicity was noted at the mid dose and above as reduced body weight gain, and reduced food and water intake. Additionally, at 135 mg/kg/day there was an increased incidence of abortions and decreased body weights. The Maternal Toxicity NOEL is 15 mg/kg/day and the Maternal Toxicity LOEL is 45 mg/kg/day based on reduced body weight gains and reduced food and water consumption. Developmental toxicity was noted in the mid dose in the form of decreased fetal body weight, increased number of runts, and increased incidence of extra and partial ribs. The Developmental Toxicity NOEL is 15 mg/kg/day and the Developmental Toxicity LOEL is 45 mg/kg/day based on decreased fetal body weights, increased number of runts and increased incidence of skeletal anomalies.

Dose and Endpoint for use in risk assessment: Developmental Toxicity NOEL = 15 mg/kg/day from the developmental toxicity study in rabbits; Developmental Toxicity LOEL = 45 mg/kg/day (basis described above).

Comments about study and/or endpoint: None

This risk assessment IS required.

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SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: Not applicable

MRID No.: Not applicable

Summary: none

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: No appropriate study was identified. The NOEL was $\geq$ 1000 mg/kg/day (Limit-Dose) in a 21-day dermal toxicity study in rabbits.

This risk assessment is NOT required.
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INHALATION EXPOSURE:

Study Selected - Guideline No.: 21-Day Inhalation Toxicity - Rat (§82-4)

MRID No.: 00153706 ✓

Summary: In a 21-day inhalation toxicity study Wistar TNO/W 74 albino rats from Winkelmann, Borchen were exposed to DIC 1468 (Metribuzin; 98.2 and 93.1% a.i.) in Ethanol-lutrol 1:1 (polyethylene glycol 400) at analytical doses ranging from 32 to 720 mg/m^3 DIC 1468 air. The Systemic Toxicity NOEL is equal to 219 mg/m^3 air (0.219 mg/L) and the Systemic Toxicity LOEL is equal 720 mg/m^3 air (0.720 mg/L) based on clinical signs of toxicity, increased liver enzyme activities and increased organ weights.

Dose and Endpoint for use in risk assessment: Systemic Toxicity NOEL is equal to 219 mg/m^3 air (0.219 mg/L); the Systemic Toxicity LOEL is equal 720 mg/m^3 air (0.720 mg/L) based on clinical signs of toxicity, increased liver enzyme activities and increased organ weights.

Comments about study and/or endpoint: None

This risk assessment is required.
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INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: Not applicable

MRID No.: Not applicable

Summary: none

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: No appropriate study was identified. The NOEL was $\geq$ 1000 mg/kg/day (Limit-Dose) in a 21-day dermal toxicity study in rabbits.

This risk assessment is NOT required.

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INHALATION EXPOSURE:

Study Selected - Guideline No.: 21-Day Inhalation Toxicity - Rat (§82-4)

MRID No.: 00153706

Summary: In a 21-day inhalation toxicity study Wistar TNO/W 74 albino rats from Winkelmann, Borchen were exposed to DIC 1468 (Metribuzin; 98.2 and 93.1% a.i.) in Ethanol-lutrol 1:1 (polyethylene glycol 400) at analytical doses ranging from 32 to 720 mg/m^3 DIC 1468 air. The Systemic Toxicity NOEL is equal to 219 mg/m^3 air (0.219 mg/L) and the Systemic Toxicity LOEL is equal 720 mg/m^3 air (0.720 mg/L) based on clinical signs of toxicity, increased liver enzyme activities and increased organ weights.

Dose and Endpoint for use in risk assessment: Systemic Toxicity NOEL is equal to 219 mg/m^3 air (0.219 mg/L); the Systemic Toxicity LOEL is equal 720 mg/m^3 air (0.720 mg/L) based on clinical signs of toxicity, increased liver enzyme activities and increased organ weights.

Comments about study and/or endpoint: None

This risk assessment is required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: Not applicable

MRID No.: Not applicable

Summary: none

Dose and Endpoint for use in risk assessment: Not applicable

Comments about study and/or endpoint: No appropriate study was identified. The NOEL was $\geq$ 1000 mg/kg/day (Limit-Dose) in a 21-day dermal toxicity study in rabbits.

This risk assessment is NOT required.

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INHALATION EXPOSURE:

Study Selected - Guideline No.: 21-Day Inhalation Toxicity - Rat (§82-4)

MRID No.: 00153706

Summary: In a 21-day inhalation toxicity study Wistar TNO/W 74 albino rats from Winkelmann, Borchen were exposed to DIC 1468 (Metribuzin; 98.2 and 93.1% a.i.) in Ethanol-lutrol 1:1 (polyethylene glycol 400) at analytical doses ranging from 32 to 720 mg/m^3 DIC 1468 air. The Systemic Toxicity NOEL is equal to 219 mg/m^3 air (0.219 mg/L) and the Systemic Toxicity LOEL is equal 720 mg/m^3 air (0.720 mg/L) based on clinical signs of toxicity, increased liver enzyme activities and increased organ weights.

Dose and Endpoint for use in risk assessment: Systemic Toxicity NOEL is equal to 219 mg/m^3 air (0.219 mg/L); the Systemic Toxicity LOEL is equal 720 mg/m^3 air (0.720 mg/L) based on clinical signs of toxicity, increased liver enzyme activities and increased organ weights.

Comments about study and/or endpoint: None

This risk assessment is required.

CANCER CLASSIFICATION AND BASIS: Metribuzin was classified as Group D, not classifiable as to human carcinogenicity. This was based on a mouse study that was negative for carcinogenicity at dosing levels up to 3200 ppm (MRID 00087795), a 1974 rat study (SPF Wistar rats) in which the observed pituitary adenomas and carcinomas were not statistically significant at dosing levels up to 300 ppm (MRID# 00061261), and a 1993 rat study (Fischer [CDF(F-344)/BR] rats) that was negative for carcinogenicity at dosing levels up to 900 ppm (MRID# 42672501).

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RfD AND BASIS: The HED RfD/QA Committee recommended that an RfD be established on the basis of a two-year feeding study in rats. Increased absolute and relative weight of thyroid, decreased lung weight in females and significant changes in T3 and T4 levels were observed in males and/or females at 30 ppm at the lowest dose tested (1.3 g/kg/day for males and 1.6 mg/kg/day in females). An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.013 mg/kg/day. Since the effects observed at the lowest dose tested were considered to be of marginal biological significance (threshold effects), the Committee did not recommend for an additional UF to compensate for the lack of a NOEL. It was also recommended to use the reproductive toxicity study with a NOEL of 1.3 mg/kg/day as a Co-critical study. However, when the chemical was submitted to the Agency RfD Work Group for verification in their meeting of February 16, 1994, the Work Group did not concur with the Health Effects Division - RfD/Peer Review Committee's position with respect to the LOEL in the chronic rat study. The Work Group felt that the lowest dose level should be defined as a NOEL and not a threshold LOEL. In their meeting of March 17, 1994, the Health Effects Division - RfD/Peer review Committee concurred with the Agency RfD Work Group's position. It should be emphasized that the only change to the RfD would be redefining the LOEL as a NOEL.

NOEL for critical study: 1.3 mg/kg/day (males)

Study Type - Guideline No.: §83-1(a)

MRID: 42672501 ✓

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Metribuzin

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
§81-1	Acute Oral	00106155	LD50 = m = 2.3 mg/kg f = 2.2 mg/kg	III
§81-2	Acute Dermal	00106149	LD50 > 20 gm/kg	IV
§81-3	Acute Inhalation	00157524	LC50 > 0.648 mg/L	III
§81-4	Primary Eye Irritation	ACC.# 112032	not an eye irritant	IV
§81-5	Primary Skin Irritation	ACC.# 112032	PIS = 0.33/8.0 not a dermal irritant	IV
§81-6	Dermal Sensitization	00106158	Not a dermal sensitizer	NA